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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,963	06/21/2005	Menachem Rubinstein	057878-16	3232
7590 David S. Resnick Nixon Peabody LLP 100 Summer Street Boston, MA 02110				
03/16/2010				
EXAMINER				
MARVICH, MARIA				
ART UNIT		PAPER NUMBER		
1633				
MAIL DATE		DELIVERY MODE		
03/16/2010		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/530,963

Applicant(s)

RUBINSTEIN ET AL.

Examiner

MARIA B. MARVICH

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 December 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 2, 5-15, 17-19 and 34-50 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2 and 35-49 is/are rejected.
- 7) ☒ Claim(s) 1, 5-15, 17-19 and 34 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 11 April 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

This office action is in response to an amendment filed 12/3/09. Claims 1, 2, 5-15, 17-19 and 34-50 are pending in the application.

Claim Objections

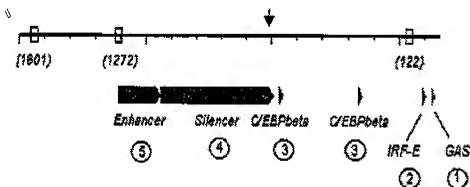
Applicants' amendment is sufficient to overcome the claim objections set forth in the office action mailed 1/21/09. **These are new objections. Dependent claims are included on the 326 as objected to as they fail to overcome the deficiencies set forth below.**

Claims 1, 2, 18, 19, 34, 44-46, 48 and 49 and 50 are objected to because of the following informalities: Upon further consideration, the scope encompassed by the claims requires clarification. As recited, it is not clear if the isolated DNA sequence of claim 1 comprises just the IL-18BP promoter sequence (SEQ ID NO:1) or SEQ ID NO:1 and SEQ ID NO:5. If it is the former, the claims are improper as "Claims in dependent form shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim. A multiple dependent claim shall be construed to incorporate by reference all the limitations of each of the particular claims in relation to which it is being considered. (37 CFR 1.75(c)". In other words, you cannot refer to a portion of an independent claim. If it is the later, then it is not clear that the isolated sequence comprises SEQ ID NO:5 as the claim recites that the isolated sequence is linked to SEQ ID NO:5 but does not indicate that it "comprises" SEQ ID NO:5. Similar amendment to claim 34 and 50 is required.

In claim 2, the claim recites, "the promoter fragment or derivative is mutated at one or more AP1 sites present in the silencer element present in the SEQ ID NO:3". First of all, the

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article "the" is cumbersome and not necessary prior to "SEQ ID NO:3". However, more to the point, it is unclear that the silencer element is in SEQ ID NO:3. The specification teaches



SEQ ID NO:3 is found at nucleotides 1151-1272, SEQ ID NO:2 from 639-1272. The silencer region according to this diagram does not fall within SEQ ID NO:3 (the large arrow is at 656). However, it does appear as if it falls within SEQ ID NO:2. Clarification is required. Similar amendment to claim 50 is required.

Claims 18, 19, 48 and 49 should recite --The recombinant virus-- as reference to previous limitations requires the article "the" as opposed to "a".

This objection is maintained for reasons of record in the office action mailed 8/6/09 and restated below. It is proper when referring to limitations previously recited to use the article "the". amendment to claims 44-46 was indicated as required. Specifically, the following amendments are required, in claim 44, --the vector-- and in claim 45 and 46--The isolated host cell--.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 35-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections necessitated by applicants' amendment.**

The dependent claims are included in the rejection because they fail to address or clarify the basis of the rejection as discussed in detail for the independent claims.

Claims 2 and 50 are vague and indefinite in that the metes and bounds of the term “derivative” are unclear. It is unclear the nature and number of steps required to obtain a “derivative” of SEQ ID NO:1. The term implies a number of different steps that may or may not result in a change in the functional characteristics of from the source that it is “derived from”.

As well, claims 2 and 50 are vague and indefinite in that the metes and bounds of the recitation, “the promoter fragment or derivative is mutated at one or more API sites present in the silencer element present in the SEQ ID NO:3”. It is unclear if the fragment or derivative thereof comprises SEQ ID NO:1. As the sequence can comprise a mutation then it cannot actually be SEQ ID NO:1. As well, claim 35 recites that this fragment or derivative consist of SEQ ID NO:2, which exacerbates the confusion.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 2, 35-40 and 42-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Novick et al (see 6,605,280, however, the rejection date is based upon WO 99/09063 which specification is the same) in view of Pance et al (*FASEB J.* (February 25, 2002), pages 631-633; see entire document). **This is a new rejection necessitated by applicants' amendment.**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103 (a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The instant claims are drawn to a vector or isolated DNA sequence comprising a functional IL-18bp promoter "fragment or derivative comprising SEQ ID NO:1". Further on this fragment or derivative is recited as consisting of SEQ ID NO:2. Hence, it appears as if there is not strict requirement that the fragment or derivative be SEQ ID NO:1. Although, this is unclear. Given that both interpretations are possible, the following art is applied.

Novick et al teach a sequence comprising SEQ ID NO:3 (see nucleotides 5448 to 568 of SEQ ID NO:5) with instant SEQ ID NO:5 at the 3' end (see nucleotides 570-620 of SEQ ID NO:5). These sequences are also found at 182-303 and 304-354 in SEQ ID NO:9. Furthermore, the sequences encode IL-18BP as recited in claim 38-39. The protein can be fused to a heterologous protein such as an immunoglobulin which encompasses claim 40 and 42 (see e.g. bridging ¶ col 12-13). Vectors i.e. aav and cells i.e. CHO are taught (see e.g. col 14, line 4-56 and col 15, line 30) as recited claims 43-47 and 49. As well, the sequences include the first introns of IL-18bp as recited in claim 36 and 37.

RESULT 1
US-09-485-632B-5
; Sequence 5, Application US/09485632B
; Patent No. 6605280
; GENERAL INFORMATION:
; APPLICANT: No. 6605280ick, Daniela
; APPLICANT: Dinarello, Charles
; APPLICANT: Rubinstein, Menachem
; APPLICANT: Kim, Soo Hyun
; TITLE OF INVENTION: Interleukin-18 Binding Proteins, their Preparation and
; TITLE OF INVENTION: Use
; FILE REFERENCE: 20993-001
; CURRENT APPLICATION NUMBER: US/09/485,632B
; CURRENT FILING DATE: 2000-10-12
; PRIOR APPLICATION NUMBER: IL98/00379
; PRIOR FILING DATE: 1998-08-13
; PRIOR APPLICATION NUMBER: 125463

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; PRIOR FILING DATE: 1998-07-22
; PRIOR APPLICATION NUMBER: 122134
; PRIOR FILING DATE: 1997-11-06
; PRIOR APPLICATION NUMBER: 121869
; PRIOR FILING DATE: 1997-09-29
; PRIOR APPLICATION NUMBER: 121639
; PRIOR FILING DATE: 1997-08-27
; PRIOR APPLICATION NUMBER: 121554
; PRIOR FILING DATE: 1997-08-14
; NUMBER OF SEQ ID NOS: 15
; SOFTWARE: PatentIn Ver. 2.0
; SEQ ID NO 5
; LENGTH: 7063
; TYPE: DNA
; ORGANISM: Homo sapiens
US-09-485-632B-5

```

Query Match 86.1%; Score 545.8; DB 3; Length 7063;
Best Local Similarity 99.6%; Pred. No. 2.3e-163;
Matches 547; Conservative 0; Mismatches 2; Indels 0; Gaps 0;

[illegible]

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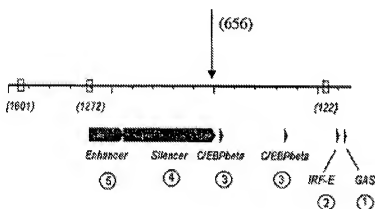
```

Qy      566  AAAAAGTGAAAGTGAAATAGAGGGTCGGGGCAGTGCTTCCCAGAAGGATTGCTCGGCAT625
          |||
Db      501  AAAAAGTGAAAGTGAAATAGAGGGTCGGGGCAGTGCTTCCCAGAAGGATTGCTCGGCAT560

Qy      626  CCTGCCCTT 634
          |||
Db      561  CCTGCCCTT 569

```

While the first 85 nucleotides of SEQ ID NO:2 are missing, it does not appear that these sequences are critical for functionality of the sequences.



Novick et al do not teach that the sequence comprises a mutation in the silencer region.

However, the art is aware of methods and outcomes of mutation of AP-1 sites found within silencer elements. For example, Pance et al teach modifications of a promoter to mutate the AP-1 site (see figure 1). As demonstrated in figure 3, the expression is highly increased in the presence of such a mutation.

In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (*Id.* At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that obviousness in part is predicated on use of particular known techniques that

are recognized as part of the ordinary capabilities of one skilled in the art. In the instant case, it is accepted that the art of record indicates that the promoter was known to comprise a silencer element at the time of filing (see Hurgin et al) and that the motivation and means to mutate silencer elements within promoters existed in order to increase efficiency of the promoter. As well, it is within the ordinary skill of the art to use available methodologies to modify sequences by applying conventional methodologies to improve existing promoters. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Novick et al (see 6,605,280, however, the rejection date is based upon WO 99/09063 which specification is the same) in view of Pance et al (*FASEB J.* (February 25, 2002), pages 631-633; see entire document) as applied to claims 2, 35-40 and 42-49 above, and further in view of Hurgin et al, (2001) *Journal of Interferon and Cytokine Research* 24:S. 73. **This is a new rejection necessitated by applicants' amendment.**

Applicants' claims are drawn to an IL-18bp promoter fragment or derivative comprising a mutation in the silencer region and further operably linked to a luciferase sequence.

The teachings of Novick et al are as above except Novick et al do not teach that the fusion protein is luciferase.

Hurgin et al. teaches a 2 kb genomic sequence upstream of the human IL-18BP gene contains a promoter and enhancer element as determined by luciferase reporter vectors. Hence Hurgin et al teach that expression of luciferase can be mediated by the IL-18bp promoter which is present in the vectors of Novick et al.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use luciferase as taught by Hurgin et al as the fusion protein in the construct as taught by Novick et al . In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (*Id.* At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on it precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (*Id.* At 1395.) In the instant case, it is well known the luciferase can be used to monitor and assess transfection, localization and success of expression of protein. As well, Hurgin et al teaches that it can be successfully expressed using the IL-18bp promoter as taught by Novick et al.

Thus, all of the elements of claims were known to one of ordinary skill in the art at the time the invention was made and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination

would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of invention. Therefore, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Primary Examiner
Art Unit 1633

/Maria B Marvich/
Primary Examiner, Art Unit 1633

